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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/549,893	09/16/2005	Shigeo Yanai	68115(46590)	7166

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EXAMINER	
SASAN, ARADHANA	

ART UNIT	PAPER NUMBER
1615	

MAIL DATE	DELIVERY MODE
08/25/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/549,893	YANAI ET AL.	
	Examiner	Art Unit	
	ARADHANA SASAN	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-9,11,12 and 23-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-9, 11-12 and 23-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/29/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. The remarks and amendments filed on 05/29/08 are acknowledged.

2. Claims 1-6, 10 and 13-22 were cancelled.

3. Claims 7-9, 11-12 and 23-28 were amended.

4. New claim 35 was added.

5. Claims 7-9, 11-12 and 23-35 are included in the prosecution.

Information Disclosure Statement

6. The information disclosure statements (IDS) submitted on 05/29/08 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97 and 1.98. Accordingly, the examiner is considering the information disclosure statement.

See attached copy of PTO-1449.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

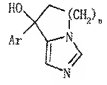
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 7-9, 11-12 and 23-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tasaka et al. (WO 02/40484) in view of Dandiker et al. (US 5,425,950).

The claimed invention is a controlled release composition for oral administration, wherein

(A) a core containing

(1) a physiologically active substance which is a compound represented by the formula:



(I)-A

where n is an integer of 1 to 3, and Ar is an aromatic ring which may be substituted, or a salt thereof, and

(2) hydrophilic polymers selected from hydroxypropylcellulose and low-substituted hydroxypropylcellulose, which is coated with

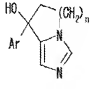
(B) a coating layer containing

(1) methacrylic acid copolymers as an enteric coating agent,

(2) talc as a lubricant, and

(3) a plasticizer selected from polyethylene glycol and triethyl citrate.

Tasaka teaches a compound of the formula:



(I)

wherein n is an integer of 1 to 3; and Ar is an optionally substituted aromatic ring, or a salt thereof (Page 4, lines 1-8). The compound (+)-6-(7-hydroxy- 6, 7-dihydro- 5H-

pyrrolo [1,2-c] imidazol-7-yl)-N-methyl-2-naphthamide is disclosed as one of the compounds (Page 6, lines 24-25). A pharmaceutical composition containing the compound, which is an antitumor agent, and which is an agent for the prophylaxis or treatment of breast cancer or prostate cancer is disclosed (Page 8, lines 6-14). Pharmaceutically acceptable carriers that are used in the composition, including an excipient, a lubricant, a binder, a disintegrating agent and a thickener are disclosed (Page 39, lines 29-33). "Preferable examples of the excipient include lactose, sucrose, D-mannitol, starch, ... Preferable examples of the lubricant include magnesium stearate, calcium stearate, talc, colloidal silica ... Preferable examples of the binder include ... hydroxypropylcellulose, hydroxypropylmethylcellulose ... Preferable examples of the disintegrating agent include starch, carboxymethyl cellulose, carboxymethyl cellulose calcium, crosscarmellose sodium, sodium carboxymethyl starch ... Preferable examples of the thickener include natural gums ... Preferable examples of the solvent include ... propylene glycol ... Preferable examples of the dispersing agent include polyethylene glycol ... Preferable examples of the solubilizer include polyethylene glycol, propylene glycol ... Preferable examples of the isotonicity agent include ... glycerine ..." (Page 40, lines 4-33). The reference also discloses that a tablet, powder, granule or capsule can be prepared by adding "an excipient, a disintegrating agent, a binder, a lubricant and the like to the compound of the present invention, and subjecting the mixture to compression molding, and where necessary, coating for masking of taste, enteric coating or coating for sustention" (Page 41, lines 12-18). The pharmaceutical preparation can be administered orally (Page 42, lines 26-

28) and a sustained release preparation can also be administered (Page 43, lines 8-9). Example 5 discloses the production of 6-(7-hydroxy- 6, 7-dihydro- 5H-pyrrolo [1,2-c] imidazol-7-yl)-N-methyl-2-naphthamide (Page 58, line 12 to Page 59, line 8).

Tasaka does not expressly teach methacrylic acid copolymers as enteric coating agents and a coating layer with a physiologically active substance.

Dandiker teaches tablet formulations where an enteric coating is applied by spraying a methacrylic acid copolymer containing solution (Col. 13, Example 9, lines 64-67). Dandiker also teaches a first active that is dispersed throughout a polymer matrix, and a second active that is dispersed throughout an excipient base. The mix with the second active "is compressed and the resulting tablets are further compression coated with the polymer matrix containing the first active" (Col. 13, Example 6, lines 12-25).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a composition comprising the compound of formula (I) and an enteric coating, as suggested by Tasaka, combine it with a methacrylic acid copolymer containing enteric coating, as taught by Dandiker, and produce the instant invention.

One of ordinary skill in the art would do this because methacrylic acid copolymers are known components of enteric coatings, as evidenced by the coating taught by Dandiker. One with ordinary skill in the art would know that the formulation taught by Tasaka can be enterically coated (Page 41, lines 12-18) and would use methacrylic acid copolymers for the enteric coating (as taught by Dandiker, (Col. 13, Example 9, lines 64-67) during the process of routine experimentation. One with

ordinary skill in the art would have a reasonable expectation of success in producing a tablet with the compound of formula (1)-A that is enterically coated.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Regarding instant claim 7, the controlled release composition is taught by the composition comprising the compound of formula (I) disclosed by Tasaka (Page 4, lines 1-8 and Page 43, lines 8-9). The physiologically active substance represented by the formula (1)-A would have been obvious over the compound of formula (I) taught by Tasaka (Page 4, lines 1-8 and Page 6, lines 24-25). The hydrophilic polymer would have been obvious over the hydroxypropylcellulose taught by Tasaka (Page 40, lines 8-10). The enteric coating would have been obvious over the enteric coating taught by Tasaka (Page 41, lines 12-18). The methacrylic acid copolymers for enteric coating would have been obvious over the enteric coating that is applied by spraying a methacrylic acid copolymer containing solution, as taught by Dandiker (Col. 13, Example 9, lines 64-67). The talc as lubricant would have been obvious over the talc taught by Tasaka (Page 40, lines 6-8). The plasticizer would have been obvious over the polyethylene glycol taught by Tasaka (Page 40, lines 4-33).

Regarding instant claims 8 and 32, the rapid release property of the physiologically active substance in the absence of the coating layer would have been

obvious over the tablet without a coating layer as disclosed in Preparation Example 2 by Tasaka (Page 76, lines 12-23). A tablet without a coating layer will intrinsically have the property of rapid release of the active substance when compared to a tablet with a coating layer.

Regarding instant claim 9, the limitation of the core as a controlled release matrix would have been obvious over the controlled release hydrophilic polymer hydroxypropylcellulose taught by Tasaka (Page 40, lines 8-10).

Regarding instant claims 11-12 and 33, the pH dependent or delayed-dissolution type water solubility of the polymer in the coating layer and the insoluble or sparingly soluble polymer in the coating layer would have been obvious over the enteric coating of the composition taught by Tasaka (Page 41, lines 12-18) in view of the methacrylic acid copolymer used as an enteric coating agent, as taught by Dandiker (Col. 13, Example 9, lines 64-67). One with ordinary skill in the art would know that enteric coating polymers are water insoluble, pH dependent, and delay the dissolution of the active ingredient until after the acidic pH of the gastric passage.

Regarding instant claim 23, the compound would have been obvious over the (+)-6-(7-hydroxy- 6, 7-dihydro- 5H-pyrrolo [1,2-c] imidazol-7-yl)-N-methyl-2-naphthamide taught by Tasaka (Page 6, lines 24-25). The hydrophilic polymer would have been obvious over the hydroxypropylcellulose taught by Tasaka (Page 40, lines 8-10). The enteric coating would have been obvious over the enteric coating taught by Tasaka (Page 41, lines 12-18). The methacrylic acid copolymers for enteric coating would have been obvious over the enteric coating that is applied by spraying a methacrylic acid

copolymer containing solution, as taught by Dandiker (Col. 13, Example 9, lines 64-67). The talc as lubricant would have been obvious over the talc taught by Tasaka (Page 40, lines 6-8). The plasticizer would have been obvious over the polyethylene glycol taught by Tasaka (Page 40, lines 4-33).

Regarding instant claim 24, the solubility of the physiologically active substance would have been obvious over the compound of formula (I) disclosed by Tasaka (Page 4, lines 1-8). The solubility of a compound is an intrinsic property of the compound and since the compound of formula (I) is taught by Tasaka, the solubility of the compound would be obvious over Tasaka.

Regarding instant claim 25, the limitation of the hydrophilic polymer used at about 3% to about 95% by weight would have been obvious over the hydrophilic polymers (hydroxypropylcellulose and hydroxypropylmethylcellulose) taught by Tasaka (Page 40, lines 8-10) and by the 70% w/w of hydroxypropyl methylcellulose (in the first polymer matrix) and 77% w/w of hydroxypropyl methylcellulose (in the second polymer matrix) as taught by Dandiker (Col. 13, Example 6, lines 12-25). One with ordinary skill in the art would find it obvious to use hydroxypropylcellulose or hydroxypropylmethylcellulose in the formulation since both are disclosed as applicable hydrophilic polymers by Tasaka.

Regarding instant claim 26, the controlled release composition coated with a coating layer which contains a physiologically active substance would have been obvious over the composition comprising the compound of formula (I) as taught by

Tasaka (Page 4, lines 1-8 and Page 43, lines 8-9) in view of the coating with a different active as taught by Dandiker (Col. 13, Example 6, lines 12-25).

Regarding instant claims 27 and 34, the use of the controlled release composition for treating prostate cancer or breast cancer would have been obvious over the pharmaceutical composition used for the treatment of breast cancer or prostate cancer as taught by Tasaka (Page 8, lines 6-14). Moreover, the use of the controlled release composition for "prevention" of prostate cancer or breast cancer is an intended use and has no significance in composition claims.

Regarding instant claims 28-30, the limitation of a different release rate of a physiologically active substance would have been obvious over the composition with the compound taught by Tasaka (Page 4, lines 1-8 and Page 43, lines 8-9) in view of the pulsed release of the first active and sustained release of the second active taught by Dandiker (Col. 13, Example 6, lines 12-25).

Regarding instant claims 31 and 35, the dissolution characteristics of the controlled release composition would have been obvious over the composition comprising the compound of formula (I) and the sustained release preparation disclosed by Tasaka (Page 4, lines 1-8 and Page 43, lines 8-9). The dissolution characteristics of a composition are an intrinsic property of the composition and since a composition comprising the compound of formula (I) is taught by Tasaka, the dissolution characteristics of the composition would be obvious over Tasaka.

Response to Arguments

Rejection of claims 1-6, 8, 14, 24 and 27 under 35 USC § 102(b)

9. In light of Applicant's amendment of claim 7 to include methacrylic acid copolymers as enteric coating agents, the rejection of 01/30/08 is withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of Dandiker et al. (US 5,425,950).

Rejection of claims 7, 9-12, 22-23 and 25 under 35 USC § 103(a)

10. Applicant's arguments, see Page 10, filed 05/29/08, with respect to the rejection of claims 7, 9-12, 22-23 and 25 under 35 USC § 103(a) as being as being unpatentable over Tasaka et al. (WO 02/40484) in view of Okada et al. (US 5,807,880) have been fully considered and are persuasive in light of the amendment of claim 7 to include methacrylic acid copolymers as enteric coating agents. The rejection of 01/30/08 is withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of Dandiker et al. (US 5,425,950).

Rejection of claims 7, 9-12, 22-23 and 25 under 35 USC § 103(a)

11. Applicant's arguments, see Page 10, filed 05/29/08, with respect to the rejection of claims 13, 15-21, 26 and 28-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tasaka et al. (WO 02/40484) in view of Fernandez et al. (US 3,696,188) have been fully considered and are persuasive in light of the amendment of claim 7 to include methacrylic acid copolymers as enteric coating agents. The rejection of 01/30/08 is withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of Dandiker et al. (US 5,425,950).

Conclusion

12. No claims are allowed.

13. Since this new rejection was necessitated by applicant's amendment, **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aradhana Sasan whose telephone number is (571) 272-9022. The examiner can normally be reached Monday to Thursday from 6:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached at 571-272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Aradhana Sasan/
Examiner, Art Unit 1615

/MP WOODWARD/
Supervisory Patent Examiner, Art Unit 1615